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O. Wada and M. Nagahashi

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# Germanium Poisoning Caused by Health Food

Osamu WADA* and Masaru NAGAHASHI**

Key words: Germanium poisoning, germanium health food, renal insufficiency of unknown origin, myopathy

## I Germanium and its background

Germanium is generally little toxic. Because of its position in the periodic table and because of the volume of its presence inside the body of organisms or because it is considered to be an element producing some essential action within the body, all kinds of studies have been conducted on its medicinal action. In the past it had been assumed to have an action leading to the increase of red blood cells. At the present time, however, this has not yet been proven.

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* Professor at the Medicine Dpt. of Tokyo University (Health Sciences). Graduated in 1960 from the Medicine Dpt. of Tokyo University; professor at the Gumma University in 1977; present position from 1983; main fields of research: environmental medicine, industrial health protection, toxicology, trace elements

** Health Science Section, Department of Medicine, Tokyo University

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Germanium came to the focus of attention because it was believed to be abundant in natural drugs. For instance, originally produced "Korean carrots" (ginseng) are reported to contain 250 - 4,000 ppm, kuko (Chinese matrimony vine) fruit 124 ppm, and shishi* 262 ppm. Because of rumors such as about low contents and low effectivity in Japan-grown ginseng the mysterious power of germanium has been the object of attention of the people at large.

While attention was being paid to these Japanese-Chinese medicines, 2- carboxyethylgermanium sesoxide (Ge-132) which is an organic germanium was synthesized by a certain laboratory in Japan. The pharmacological effect was studied for many years by various research institutions and the product was proven to have for example an interferon-inducing action, a macrophage-activating action and an immunity-adjusting action. Because of these, one pointed to the possibility of antitumor action, and tests were conducted. Spirogermanium which is an organic germanium acting as an obstacle to nucleic acid metabolism is being tested abroad. As public concern about cancer is rising, germanium seems to know a boom as a mysterious substance having an health-enhancing action.

At the present time more than 60 companies in Japan are marketing over 60 types of germanium products labelled germanium health food. They are sold in the form of mineral source water, drinking water, drink components, tablets, foodstuffs, capsules, grains, powder and pills. Germanium is widely divided into germanium oxides ($GeO_2$), analogues of the above Ge-132 and spiruline (algae) components. The germanium

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* translator's note: reading and meaning uncertain (詞子)

contents vary greatly, ranging from 3 ppm to $5 \times 10^4$ ppm. It goes without saying that at the present time these products are not sold as pharmaceuticals.

## II Occurrence of germanium poisoning

It seems that germanium health foods began to be sold about 10 years ago. The first report of poisoning thought to be caused by germanium health food was made in 1982. As far as we have been able to check there have been up to 23 cases of poisoning since in medical journals.

In view of the analysis of these cases, it would seem that if one considers the quantities of marketed products and the number of users of the same there could be a fair number of poisoning cases attributed to unknown causes or just overlooked. This is for us the occasion to consider and report the cases systematically and to call for the attention of physicians at large.

## III Characteristic clinical images of germanium poisoning

In Table 1 we tabulated the clinical images of 23 cases of germanium poisoning. There is no difference based on sex or age. This is one of the important characteristics of this exogenous poisoning disease. As for the age we see that the disease afflicts infants as well as the elderly. In the case of infants the most common cause is exaggerated love on the part of the mother wanting to enhance her child's health.

There are a few main symptoms: (1) renal insufficiency or renal trouble of unknown origin, (2) anemia, and more particularly orthospheric orthopigmentary anemia, (3) myopathy, and more especially drop in muscular power, and muscular atrophy (often closely approaching types). Frequently, one sees also numbness or perception trouble, abnormal perception caused by peripheral nervous disorders. Often, the early symptoms are a suddenly appearing lack of appetite, nausea, vomiting, general fatigue going to emaciation.

One sees multiple organ troubles which are characteristics of this poisoning disease. There is trouble of the hematopoietic system and of the digestive organs where there are cells having a fast metabolic rotation. It is also extremely interesting to note that one sees renal trouble characterized by matters harmful to renal discharge. It accompanies nervous and muscular trouble. This is a clinical picture impossible to explain in a systematic disease.

One should also consider that these symptoms are grasped as characteristic clinical units not seen in poisoning by other metals, and it is clearly possible to treat this condition as a definite disease.

At the time of the report and survey, 6 of the 23 cases had died. If we admit that these deaths are really caused by germanium health food, then we face a very serious problem. Table 2 shows the examination results. The following is most interesting to observe.

(1) Although the blood urea nitrogen (BUN), serum uric acid and creatine values are extremely high, very little is seen in the urine. Although renal insufficiency is noted in the blood examinations of the early and middle periods, most of the urine protein, urine occult blood tests are negative. One may similarly say that one sees an increase in urine volume believed to cause problems in the removed region of the renal tubules as well as a drop in the specific urine weight.

(2) In all cases, one sees a fair degree of anemia (hemoglobin concentration of 7 - 11.2 g/dL) which is of the orthospheric, orthopigmentary type.

(3) Often myopathy is reflected or the CPK value also is high. When the kidneys were examined through autopsies or live examinations, interstitial nephritis was central, and one notes renal tubule degeneration. More particularly, we noted granular matters (darkly dyed grains inside the mitochondriae) stained dark purple with PAS stain in the epithelium of the receded region of the renal tubules. There was little change in the glomeruli. In the muscles one noted fatty atrophic muscle disease and myogenic atrophy.

IV The state of germanium consumption and the toxicity values

The amount of germanium consumption of 18 subjects whose amount of consumption was known ranged from 35 to 2,000 mg per day, with an average of 260 mg. The period of consumption ranged from 5 months to 6 years, the average being 16 months.

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Table 1 Clinical image of 23 germanium poisoning cases p.1930

| Facts | Frequency and other annotations |
|---|---|
| (sex) males: 10; females: 10; unknown: 3 | |
| (age) four - sixty | |
| (symptoms) | |
| (1) renal insufficiency, renal trouble | 100% |
| (2) anemia | 100% |
| (3) drop in muscular power, muscular atrophy | 43% |
| (4) peripheral nervous trouble | 35% |
| (5) general fatigue, emaciation | 31% |
| (6) nausea, vomiting, no appetite | 31% |
| (result) death | 6 cases on 23 cases |
| (germanium ingestion) | |
| daily intake | 35 - 2,000 mg (average of 260 mg) |
| period of ingestion | 5 months - 6 years (average of 16 months) |

Table 2 Results of the examination of 23 germanium poisoning patients p.1931

| Points examined | Value and frequency |
|---|---|
| (urine) | |
| normal | 78% |
| albumen positive | 9% |
| occult blood positive | 4% |
| unknown | 13% |
| (anemia) | |
| frequency | 100% |
| observations | orthospheric orthopigmentary anemia |
| Hb | 7.1 ~ 11.2 g/dL |
| (renal function and such) | |
| high blood urea nitrogen value | frequency: 100%<br>value: 30 - 127 mg/dL |
| high serum creatine value | frequency: 100%<br>value: 1.6 ~ 8.3 mg/dL |
| high serum uric acid value | frequency: 80%<br>value: 3.8 - 20.4 mg/dL |
| high serum CPK value | frequency: 70%<br>value: 3 ~ 1,260 IU/L |
| (biopsy/autopsy results) | |
| kidneys | interstitial nephritis, renal tubule degeneration<br>grains inside epithelium of receded region of renal tubules |
| muscle | fatty accumulation myopathy<br>muscular atrophy (mainly myogenic, sometimes also neurogenic) |

The most frequent purpose of consumption was health enhancement-nutrition strengthening for 9 out of 23 subjects (39%), followed by hepatitis treatment in 8 cases (35%) and then by fatigue restoration, diabetes treatment, thyroid gland cancer treatment in one case each. For 3 subjects, the purpose was unknown. We examined whether or not there had been kidney function trouble prior to consumption. There had been no trouble at all although the situation could not be known in a few cases.

By the existing germanium toxicity values, the 50% lethal dose which represents an acute toxicity value was as high as 3.7 g/kg for rats given orally germanium oxide, and 5.4 ~ 6.3 g/kg for mice. This shows that the level of acute toxicity is low. In subacute toxicity tests, we injected germanium oxide hypodermically for 35 days in rats at the rate of 75 mg/kg per day. The weight increase of the animals was inhibited. One noted also an increase in urine and a drop in its specific weight. At 150 mg/kg/day about one-fifth of the rats died. In chronic poisoning tests based on germanium dioxide and similarly conducted by injecting rats hypodermically, one noted that the weight increase of the animals was inhibited with 12.5 mg/kg/day for 90 days. Rats given to drink water containing 5 ppm germanium were noted to live less long, and one observed 90% protein urine. If one calculates that the germanium dose is 369.2 μg/kg/day and makes a conversion to humans with a body weight of 50 kg, the daily dose will be 18.5 mg. It is shown that if this amount is regarded as an approximate lifetime consumption (or a 2-year rat life) there will be kidney trouble.

In other tests, rats were reared for 13 weeks on feed or drinking water supplemented with germanium dioxide. In the former group, 50% of the individuals died with 1,000 ppm, and in the latter 50% died with 100 ppm. The germanium consumptions at this time are estimated at 60 mg/kg/day and 11.3 mg/kg/day respectively. These amounts correspond respectively to 3,000 mg/day, 565 mg/day for human subjects with a body weight of 50 kg. It would translate into a 50% mortality for human subjects in 13 weeks. The figures are not that much different from the amounts consumed by the above 23 poisoning cases.

## V Proof that germanium is the cause

The clinical observations of the pathologic cases reported so far suggest rather strongly that these cases represent germanium poisoning. Large amounts of germanium were detected in the hair and other samples taken from deceased patients subjected to autopsy and from surviving patients.

Larger-scale epidemiological surveys are needed to prove with more certainty the cause-effect relationship. However, reproducing the effects through animal tests constitutes also an important proof. Several reports of animal tests supporting the germanium causality have recently been published in Japan (Table 3). The data seem to indicate that rats are more sensitive than mice. It was shown in chronicity tests p.1932 that with an oral administration of 6.7 mg/kg/day of germanium during 10 months half of the rats had evident renal trouble. In subacute toxicity tests a 75 mg/kg/day administration brought about renal

trouble is about 8 - 10 weeks. If one converts the body weights, this consumption would correspond to daily doses of 335 mg and 3,750 mg respectively with regard to a human subject of 50 kg and is about at the same ingestion level as for the above intoxication patients. A more important thing is that the results yielded by inspections are completely the same as in human poisoning cases. One sees the same renal insufficiency with little urine change, the same anemia, the same drop in urine osmosis pressure. Pathological examinations reveal the same renal tubule degeneration affecting mainly the receded region of the renal tubules and the same intracellular grain appearance as in humans. The abnormality of the glomeruli is light but the same interstitial alterations are seen, and the muscles yield the same observations. With regard to germanium, the observations reveal clearly a response relationship to the treatment.

In other words, if in animal tests one considers the amounts (of germanium) and the abnormality particulars one may say that there is clear similarity to the human poisoning cases.

In chronicity tests conducted on rats with a 1.25 mg/kg/day dose, no abnormality was noted up to 10 months. If for the time being we assume such dose to have no effect, then the daily volume tolerable by human beings would be 12.5 μg/kg/day which means 625 kg for a 50 kg human subject. If rats have the same sensitivity as people, a daily germanium intake of 62.5 mg should be the maximum tolerable dose for a human subject of 50 kg.

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Table 3 Outline of animal tests on germanium ($GeO_2$)

| Person reporting | Mode of administration to animal | Amount of daily ingestion (in Ge terms) | Period | Results | | | |
|---|---|---|---|---|---|---|---|
| | | | | Body weight | Urine | Blood | Pathology |
| Matsusaka, Fujii et al. (Osaka Hospital) | rats drinking water | 1.25 mg/kg/day (0.89 - 1.38) | October | normal | normal | normal (BUN, Cr) | normal |
| | | 6.7 mg/kg/day (4.19 - 14.3) | October | increase inhibited (3/4) | drop in osmosis pressure only | BUN rise (2/4) Cr rise (2/4) | kidney: renal tubule trouble interstitial nephritis<br>muscle: cell infiltration fragmentation |
| Onoyama, Sauchi et al. (Kyushu University) | rats feed | 18.8 mg/kg/day | 8-10 weeks | normal | normal | normal | normal |
| | | 37.5 mg/kg/day | 8-10 weeks | some inhibition | normal | normal | normal |
| | | 75 mg/kg/day | 8-10 weeks | inhibition | normal | BUN rise GOT rise Ht drop | kidney: vacuolar degeneration of renal tubules (mainly receded region) appearance of grains |
| Okagawa, Okada et al. Tokushima University) | mouse through stomach tube | 130 mg/kg/day | 35 days | decrease | normal | | kidneys: renal tubules degeneration (vacuolation)<br>muscle: no obvious change |
| | | 7 mg/kg/day | 250 days | normal | normal | | kidney: lymphocyte infiltration (1/3) renal tubules degeneration (1/3) |
| Wada, Yamasaki (Tokyo University) | rats hypodermic injection | 2.5 mg/kg/day | 13 weeks | normal | urine increase only | | muscle: no obvious change |
| | | 12.5 mg/kg/day | 13 weeks | some inhibition | urine increase only | | liver, heart and kidneys somewhat hypertrophied |

This amount is the ordinary dose of germanium taken by regular users. It is presently at the very limit. If one considers the popularity of germanium and the large proportion of users, one might think that the number of poisoning cases is small.

An analysis of foodstuffs reveals that ordinary food articles contain from a few ppb to 10 ppm of germanium. The daily germanium intakes due to ordinary human food differ according to the reporting sources. They may be assumed to range from 10 to 100 μg. There are even reports of daily ingestions of 400 - 3,500 μg.

VI Verifying the taking or no taking of germanium when diagnosing renal insufficiency of unknown origin concomitant to anemia and to drop in muscular strength

We explained above the poisoning cases so far believed to be caused by germanium contained in health food. Fairly characteristic symptoms and discoveries have appeared. One noted renal insufficiency in high BUN-creatine-uricacidemia patients suffering also from anemia, a drop in muscular power, muscular atrophy, peripheral nervous trouble.

If relative to all the above symptoms one does not see much noteworthy in the urine, one should by all means consider the possibility of germanium poisoning. The reason is that it is very easy to overlook the poisoning.

I earnestly hope that the actual situation will be examined and researched very speedily, and that social measures will be taken soon.

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